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Document Number 2

Entry 2 of 2

File: USPT

Jan 28, 1997

DOCUMENT-IDENTIFIER: US 5597807 A

TITLE: Quinoa saponin compositions and methods of use

ABPL:

Novel Quinoa saponin pharmaceutical compositions are disclosed. The compositions are useful as immunological adjuvants, to stimulate nonspecific immunity, as well as to enhance an immunological response to a selected antigen. The Quinoa saponin compositions can also be used to enhance mucosal absorption of a drug administered therewith.

BSPR:

The present invention is based on the surprising discovery that Quinoa saponins are able to act as both immunological and absorption adjuvants to enhance immune responses and mucosal absorption, respectively, to a substance coadministered therewith. The discovery is particularly unexpected in light of the prior art reports that Quinoa saponins lack adjuvant activity. The invention is environmentally desirable because it provides for the use of Quinoa by-products, such as the hulls, which are currently discarded due to the bitterness conferred by the high saponin content.

DEPR:

An "antigen" refers to a molecule containing one or more epitopes that will stimulate a host's immune system to make a secretory, humoral and/or cellular immunological response. The term denotes both subunit antigens, i.e., antigens which are separate and discrete from a whole organism with which the antigen is associated in nature, as well as killed, attenuated or inactivated bacteria, viruses, parasites or other microbes. Antibodies such as anti-idiotypic antibodies, or fragments thereof, and synthetic peptide mimotopes, which can mimic an antigen or antigenic determinant, are also captured under the definition of antigen as used herein. Similarly, an oligonucleotide or polynucleotide which expresses an antigen or antigenic determinant in vivo, such as in gene therapy and DNA immunization applications, is also included in the definition of antigen herein.

DEPR:

An "absorption adjuvant" refers to a Quinoa saponin which enhances the absorption of an accompanying substance, such as a drug, in the host to which it is administered. The Quinoa saponin can be incorporated into or administered with the substance of interest either in the same composition or in a separate composition which is delivered either simultaneously, prior to or subsequent to administration of the substance of interest. Generally, absorption will be enhanced through mucosal membranes in vertebrate subjects. However, the Quinoa saponin compositions will also be useful to enhance permeability through plant and insect membranes, e.g., for increasing the uptake of herbicides and fertilizers through the

leaves and roots in plants and for enhancing the uptake of pesticides and other insecticides, including bacteria, in insects, such as by permeabilization of cells of the trachea or other membranes.

DEPR:

Central to the present invention is the discovery that Quinoa saponin compositions can promote production of immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies and enhance both humoral and secretory immune responses in a vertebrate subject when administered with a selected antigen. Additionally, the Quinoa saponins enhance nonspecific immunity and cause increased absorption through mucosal membranes.

DEPR:

Secretory immunity is thought to be largely mediated by IgA antibodies. In particular, secretory IgA serves to block the action of antigens that colonize mucosal surfaces. Thus, IgA plays a significant role in resistance to reinfection by pathogens, such as viruses, which replicate in mucosal membranes, especially those in the gastrointestinal and upper respiratory tract. Such organisms include rhinoviruses, influenza viruses, coronaviruses, parainfluenza viruses, respiratory syncytial virus, herpesviruses, adenoviruses, rhabdoviruses, paramyxoviruses, orthomyxoviruses, rotaviruses and Norwalk-like viruses. Additionally, IgA blocks the action of a number of gram positive and gram negative bacteria, parasites and protozoa, including such microbes as Salmonella, campylobacteria, cryptosporidium, isospora, Eimeria, helminths, and the like.

DEPR:

Similarly, IgA can prevent the passage of organisms through mucosal surfaces to the systemic circulation. This is of particular importance with bacteria, a number of which penetrate through damaged tissue and can cause bacteremia. Examples of organisms which initially infect mucosal surfaces and then pass into the systemic circulation include those bacteria and viruses described above, as well as the picornaviruses, poxviruses, flaviviruses, orbiviruses and alphaviruses. Serum antibodies, such as IgG, often do not provide protection of the mucosal surfaces.

DEPR:

Systemic antibodies, such as serum IgG, however, do play a significant role in neutralizing infectivity of invading organisms and promoting aggregation and clearance of pathogens, such as viruses that have a viremic mode of spread. Thus, the ability of the Quinoa saponins to augment both IgG and IgA production against selected antigens provides a powerful tool against infection by a wide variety of organisms.

DEPR:

Accordingly, as is evident, the Quinoa saponins can be used as immunological adjuvants in vaccine compositions for a variety of purposes. For example, the Quinoa saponins can be used in compositions for immunizing a vertebrate subject against a selected pathogen or against a subunit antigen derived therefrom, or for priming an immune response to a particular antigen or, for example, stimulating an immune response against a desired hormone for e.g., reproductive purposes such as fertility control and immunological sterilization. The compositions can also be used to stimulate nonspecific immunity. If used for this purpose, a specific antigen need not be present or coadministered with the Quinoa saponin adjuvants. Antigens, when administered with the Quinoa pharmaceutical compositions, can be derived from a wide variety of viruses, bacteria, fungi, plants, protozoans and other parasites. Such antigens can be derived from, e.g., any of the various species of Pasteurella, Actinobacillus, Haemophilus, Salmonella, Eimeria, and

the like, as well as those viruses specified above, including, e.g., rotaviruses (including canine, feline, bovine, porcine, equine and human rotaviruses), herpesviruses such as BHV-1, EHV-1, PRV, Parvovirus, rabiesvirus, influenza viruses (including canine, feline, bovine, porcine, equine and human influenza), parainfluenza viruses (also including canine, feline, bovine, porcine, equine and human parainfluenza), hepatitis viruses, HIV, coronaviruses (including canine, feline, bovine, porcine, equine and human coronaviruses), and the like. Similarly, antibody responses to tumor antigens, hormones, hormone analogs, and so forth, will also be enhanced by use of the Quinoa compositions herein described.

DEPR:

The antigen can be a protein, polypeptide, antigenic protein fragment, oligosaccharide, polysaccharide, or the like. Similarly, an oligonucleotide or polynucleotide, encoding a desired antigen, can be administered with the Quinoa saponin adjuvants for in vivo expression. In particular, the increased mucosal absorption caused by the saponin compositions aids the uptake of DNA into cells and nuclei and hence increases the efficiency of DNA immunization.

DEPR:

The mode of administration of the Quinoa saponin compositions will vary according to the intended use. For example, if used as immunological adjuvants (e.g., in the case of a vaccine) and systemic immunity is required, the Quinoa saponin compositions will generally be administered parenterally, usually by intramuscular injection. If mucosal immunity is required, the Quinoa saponin will generally be administered enterally, usually by oral dosing or inhalation. Other modes of administration, however, such as intradermal, intraperitoneal and intravenous injection, are also acceptable. The subject is immunized by administration of at least one dose, and preferably two or more doses. Moreover, the subject may be administered as many doses as is required to enhance immunity to the pathogen in question.

DEPR:

FIGS. 2 and 3 show that the administration of Quinoa saponins induced higher primary serum IgG and IgA responses to CTX than the administration of Quillaja saponins or the antigen alone. The group 2 animals that received Quinoa saponins a total of six times were found to have a strong secondary response to the antigen. This may be due to an increase in gut permeability caused by the Quinoa saponin adjuvant.

DEPR:

FIGS. 4 and 5 show that oral administration of CTX together with either Quillaja or Quinoa saponins, followed by two additional saponin treatments 3 and 6 days later, induced a higher IgG intestinal response to the antigen. The administration of Quinoa saponins a total of six times induced the highest intestinal IgA response. Intestinal immune responses are of importance to protection against disease since many infectious organisms either colonize the mucosa of the intestine and the lung or gain access to the systemic circulation through these surfaces. Secretory IgA are the primary defense mechanism of the gut. Such IgA responses have not heretofore been reported for Quillaja.

Main Menu	Search Form	Result Set	Show S Numbers	Edit S Numbers	Referring Patents				
First Hit		Previous Document		Next Document					
Full	Title	Citation	Front	Review	Classification	Date	Reference	Claims	KWIC

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Main Menu	Search Form	Result Set	Show S Numbers	Edit S Numbers	Referring Patents
First Hit		Previous Document			Next Document
Full	Title	Citation	Front	Review	Classification
Date	Reference	Claims	KWIC		

Document Number 1

Entry 1 of 2

File: USPT

Nov 18, 1997

DOCUMENT-IDENTIFIER: US 5688772 A

TITLE: Quinoa saponin compositions and methods of use

BSPR:

The present invention is based on the surprising discovery that Quinoa saponins are able to act as both immunological and absorption adjuvants to enhance immune responses and mucosal absorption, respectively, to a substance coadministered therewith. The discovery is particularly unexpected in light of the prior art reports that Quinoa saponins lack adjuvant activity. The invention is environmentally desirable because it provides for the use of Quinoa by-products, such as the hulls, which are currently discarded due to the bitterness conferred by the high saponin content.

DRPR:

FIG. 7 is a bar graph showing the effect of Quinoa saponins (Sp) on mucosal absorption of radiolabeled human serum albumin (HSA) as assessed by monitoring the presence of labeled HSA in liver, spleen, kidneys, heart and lungs, in the presence and absence of Quinoa saponins. Each point in the figure represents the mean of three mice.

DRPR:

FIGS. 8A-8C show the effect of Quinoa saponins on mucosal absorption of radiolabeled human serum albumin (HSA) as assessed by monitoring the presence of labeled HSA in blood (FIG. 8A); liver (FIG. 8B) and spleen (FIG. 8C), in the presence (.box-solid.) and absence (solid triangle) of Quinoa saponins. Each point in the figure represents the mean of three mice.

DEPR:

An "antigen" refers to a molecule containing one or more epitopes that will stimulate a host's immune system to make a secretory, humoral and/or cellular immunological response. The term denotes both subunit antigens, i.e., antigens which are separate and discrete from a whole organism with which the antigen is associated in nature, as well as killed, attenuated or inactivated bacteria, viruses, parasites or other microbes. Antibodies such as anti-idiotypic antibodies, or fragments thereof, and synthetic peptide mimotopes, which can mimic an antigen or antigenic determinant, are also captured under the definition of antigen as used herein. Similarly, an oligonucleotide or polynucleotide which expresses an antigen or antigenic determinant in vivo, such as in gene therapy and DNA immunization applications, is also included in the definition of antigen herein.

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host to which it is administered. The Quinoa saponin can be incorporated into or administered with the substance of interest either in the same composition or in a separate composition which is delivered either simultaneously, prior to or subsequent to administration of the substance of interest. Generally, absorption will be enhanced through mucosal membranes in vertebrate subjects. However, the Quinoa saponin compositions will also be useful to enhance permeability through plant and insect membranes, e.g., for increasing the uptake of herbicides and fertilizers through the leaves and roots in plants and for enhancing the uptake of pesticides and other insecticides, including bacteria, in insects, such as by permeabilization of cells of the trachea or other membranes.

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Central to the present invention is the discovery that Quinoa saponin compositions can promote production of immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies and enhance both humoral and secretory immune responses in a vertebrate subject when administered with a selected antigen. Additionally, the Quinoa saponins enhance nonspecific immunity and cause increased absorption through mucosal membranes.

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human rotaviruses), herpesviruses such as BHV-1, EHV-1, PRV, Parvovirus, rabiesvirus, influenza viruses (including canine, feline, bovine, porcine, equine and human influenza), parainfluenza viruses (also including canine, feline, bovine, porcine, equine and human parainfluenza), hepatitis viruses, HIV, coronaviruses (including canine, feline, bovine, porcine, equine and human coronaviruses), and the like. Similarly, antibody responses to tumor antigens, hormones, hormone analogs, and so forth, will also be enhanced by use of the Quinoa compositions herein described.

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DEPR:

This example shows the effect of Quinoa saponins on mucosal absorption of a coadministered drug. The effect was evaluated by following the mucosal uptake and biodistribution of radiolabelled antigen and proceeded as follows.

DEPR:

Three mice from each group were euthanized at each time point, as shown in FIG. 7. Liver, spleen, kidney, heart and lung tissue samples were collected and evaluated by measuring radioactivity in the samples using a .gamma.-counter. As shown in FIG. 7, the presence of Quinoa saponins in the preparation dramatically increased the levels of HSA in the tissue samples, indicating increased mucosal absorption of the preparation.

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